MINI-REVIEW

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Protective and therapeutic effects of exercise on stress-induced memory impairment

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Abstract

The objective of this paper was to systematically evaluate the potential preventive and therapeutic effects of exercise in attenuating stress-induced memory impairment. A systematic review was employed, searching PubMed, PsychInfo, Sports Discus and Google Scholar databases. For eligibility, studies had to be published in English, employ an experimental design, have the acute or chronic bout of exercise occur prior to, during or after the stressor, implement a psychophysiological stressor, and have an assessment of memory function occurring after the stressor. In total, 23 studies were evaluated, all of which were conducted among animal models. All 23 studies employed a chronic exercise protocol and a chronic stress protocol. Eight studies evaluated a preventive model, three employed a concurrent model, ten studies employed a therapeutic model, and two studies evaluated both a preventive and therapeutic model within the same study. Among the eight studies employing a preventive model, all eight demonstrated that the stress regimen impaired memory function. In all eight of these studies, when exercise occurred prior to the stressor, exercise attenuated the stress-induced memory impairment effect. Among the ten studies employing a therapeutic model, one study showed that the stress protocol enhanced memory function, one showed that the stress protocol did not influence memory, and eight demonstrated that the stress regimen impaired memory function. Among the eight studies showing that the stress protocol impaired memory function, all eight studies demonstrated that exercise, after the stressor, attenuated stress-induced memory impairment. Within animal models, chronic stress is associated with memory impairment and chronic exercise has both a preventive and therapeutic effect in attenuating stress-induced memory impairment. Additional experimental work in human studies is needed. Such work should also examine acute exercise and stress protocols.

Introduction

The prophylactic and treatment effects of exercise on various chronic diseases is well established [1]. Additionally, exercise can also help to prevent a host of cardiometabolic-related conditions (e.g., diabetes, early mortality) [2, 3]. Emerging work also demonstrates that, exercise, prior to a psychophysiological stressor [herein focused on toxic stress (not eustress)] [4], can mitigate the negative effects of the stressor. For example, we showed that acute exercise, occurring immediately before viewing emotionally charged, negatively valenced images, helped facilitate emotional regulation [5]. This "exercise preventive paradigm" has also been corroborated with other emotional regulation studies [6, 7].

This *exercise preventive paradigm* effect may also have implications in memory function. Psychophysiological stressors, such as forced social participation in a verbal presentation task, may have a negative effect on memory function [8–14]. Notably, this stress-memory relationship is thought to follow an inverted U-shaped relationship [15]. See Fig. 1 (and the Discussion section) for a schematic on the potential underlying mechanisms through which stress (both acute and chronic) may influence memory function. To our knowledge, however, there are no published reviews comprehensively evaluating the literature regarding the

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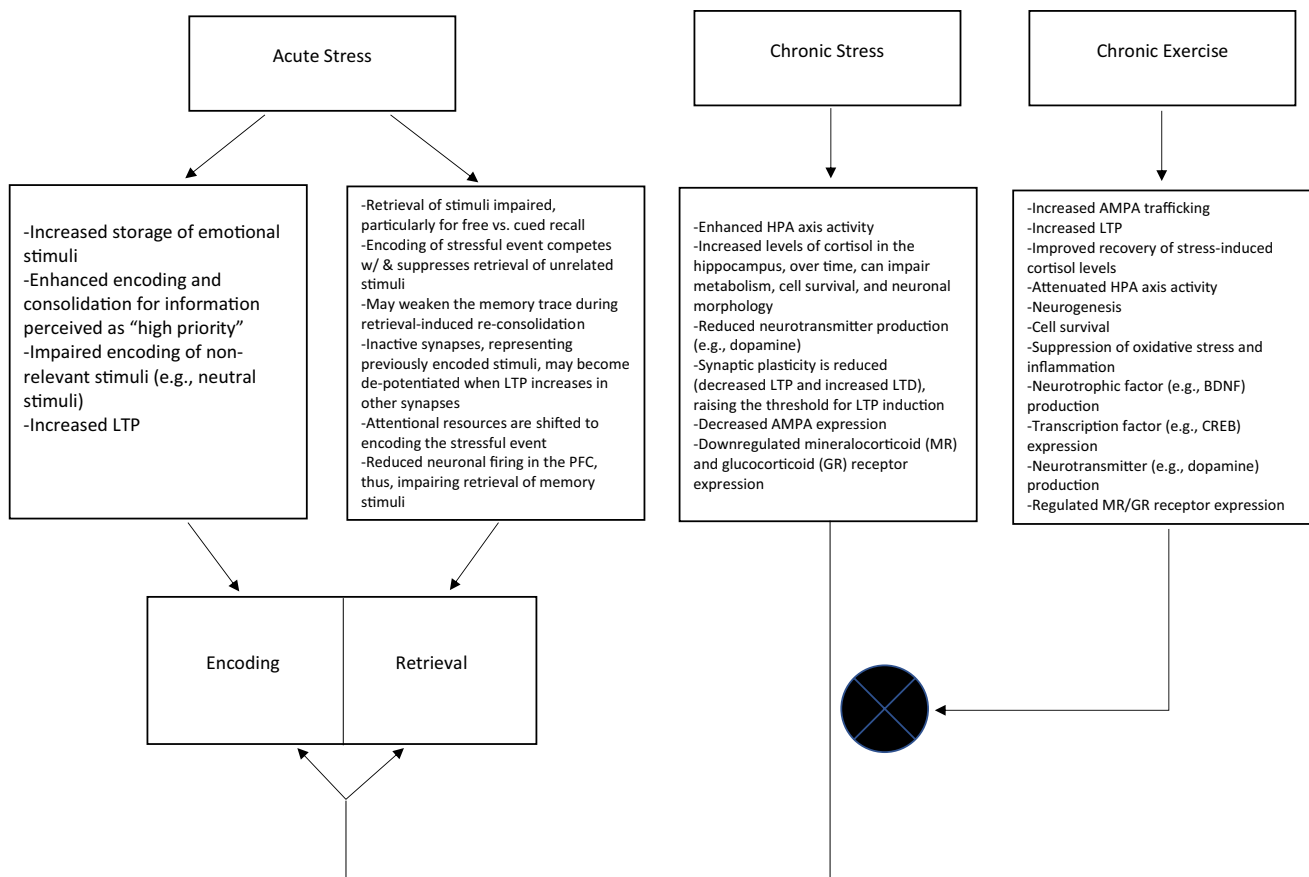
Acute Stress

-Increased storage of emotional stimuli
-Enhanced encoding and consolidation for information perceived as "high priority"
-Impaired encoding of non-relevant stimuli (e.g., neutral stimuli)
-Increased LTP

-Retrieval of stimuli impaired, particularly for free vs. cued recall
-Encoding of stressful event competes w/ & suppresses retrieval of unrelated stimuli
-May weaken the memory trace during retrieval-induced re-consolidation
-Inactive synapses, representing previously encoded stimuli, may become de-potentiated when LTP increases in other synapses
-Attentional resources are shifted to encoding the stressful event
-Reduced neuronal firing in the PFC, thus, impairing retrieval of memory stimuli

Chronic Stress

-Enhanced HPA axis activity
-Increased levels of cortisol in the hippocampus, over time, can impair metabolism, cell survival, and neuronal morphology
-Reduced neurotransmitter production (e.g., dopamine)
-Synaptic plasticity is reduced (decreased LTP and increased LTD), raising the threshold for LTP induction
-Decreased AMPA expression
-Downregulated mineralocorticoid (MR) and glucocorticoid (GR) receptor expression

Chronic Exercise

-Increased AMPA trafficking
-Increased LTP
-Improved recovery of stress-induced cortisol levels
-Attenuated HPA axis activity
-Neurogenesis
-Cell survival
-Suppression of oxidative stress and inflammation
-Neurotrophic factor (e.g., BDNF) production
-Transcription factor (e.g., CREB) expression
-Neurotransmitter (e.g., dopamine) production
-Regulated MR/GR receptor expression

Encoding   **Retrieval**

Fig. 1 Schematic indicating potential mechanisms through which acute stress may enhance memory, detrimental effects of chronic stress on memory, and how exercise may attenuate stress-induced memory impairment. The *circular crossed symbol* denotes that chronic exercise attenuates the chronic stress mechanisms

potential protective and/or therapeutic effects of exercise on mitigating stress-induced memory impairment [16], which was the purpose of this brief systematic review. The plausibility for exercise to attenuate stress-induced memory impairment is also shown in Fig. 1 (and further addressed in the Discussion section).

Methods

Studies were identified using electronic databases, including PubMed, PsychInfo, Sports Discus, and Google Scholar. We employed the computerized searches on April 25, 2018, identifying articles published prior to this date (no restriction was placed on how far back the study was published). The search terms included exercise, physical activity, stress, psychophysiological, rescue, preventive, treatment, therapeutic, psychological, memory, and cognition. To be eligible for inclusion in this systematic review, studies had to be published in English, employ an experimental design (cross-sectional designs on this topic were not eligible) [17], have

the acute or chronic bout of exercise occur prior to, during, or after the stressor, implement a toxic psychophysiological stressor (pharmaceutical agent or ischemia-induction were not eligible [18–22], mild forms of the stressor were not eligible [23], and evaluating individuals without experimentally manipulating stress were not eligible) [24], and have an assessment of memory function that occurred after the stressor. To provide a comprehensive assessment on this topic, we applied no restriction on whether the study was conducted in humans or animal models. In total, 24 studies met our criteria. However, two appeared to be duplicate studies [25, 26], and thus, one was removed. As noted in Table 1, 23 studies were evaluated herein.

Results

Table 1 displays the extraction table for the evaluated studies. All were experimental studies conducted in an animal model. The stress protocol across the studies varied, including maternal separation, loud noise exposure,

Table 1 Extraction table of the evaluated studies

Study	Animal/human	Subject characteristics	Study design	Preventive/therapeutic	Stress protocol	Exercise protocol	Memory assessment	Main findings	Speculated mechanisms
Grace (2009) [56]	Animal	Sprague-Dawley rats	Experimental	Therapeutic	Deprived from their mothers for 3 h/day for 12 days	Voluntary access to running wheels for 20 days after the maternal separation	Morris water maze, object recognition	Maternal separation did not impair memory. Exercise, however, improved memory function	N/A
Mello (2009) [57]	Animal	Wistar rats (3–4 months)	Experimental	Therapeutic	Deprived from their mothers for 3 h/day during first 10 days of life	At day 45, engaged in forced treadmill exercise; 50 min/day, 5 days/week, 8 total weeks	Morris water maze, object recognition, inhibitory avoidance	Exercise reversed the deficit of inhibitory avoidance and reduced the deficit of spatial memory	Exercise may attenuate HPA-axis activity
Makena (2012) [58]	Animal	Sprague-Dawley rats	Experimental	Therapeutic	Deprived from their mothers for 3 h/day for 12 days	Voluntary access to running wheels for ~20 days after the maternal separation	Objective recognition task	Maternal separation enhanced memory function. Maternal separation also prevented exercise-induced MAPK/ERK signaling	N/A
Kim (2013) [59]	Animal	Sprague-Dawley rats	Experimental	Therapeutic	95 dB supersonic machine sound (1 h/day) during pregnancy	After delivery, rat pups exercise on the treadmill for 30 min/day for 7 days, starting 4 weeks after birth	Radial 8-arm maze test	Stress protocol suppressed neurogenesis in the offspring and also impaired memory. Exercise attenuated these effects. Mild-intensity exercise was more effective than high-intensity exercise	Exercise-induced neurogenesis

Table 1 (continued)

Study	Animal/human	Subject characteristics	Study design	Preventive/therapeutic	Stress protocol	Exercise protocol	Memory assessment	Main findings	Speculated mechanisms
Kim (2013) [60]	Animal	Sprague-Dawley rats	Experimental	Therapeutic	Foot shocks, 3 times/day, for 7 consecutive days	4 weeks of treadmill exercise, 30 min/day	Radial 8-arm maze test	Stress protocol impaired memory, suppressed cell proliferation in the hippocampus, which was attenuated with exercise	Exercise-induced cell proliferation in the dentate gyrus
Radahmadi (2013) [25]	Animal	Wistar rats	Experimental	The exercise training and stress protocol occurred concurrently	Restrained in Plexiglass cylinder for 6 h/day for 21 days	Treadmill running, 1 h/day, for 21 days	Passive avoidance learning test	Although exercise was effective in enhancing memory, exercise was not effective in improving passive avoidance acquisition and retention when exposed to the stress protocol	N/A
Castilla-Ortega (2014) [61]	Animal	C57BL/6 J	Experimental	Preventive	Chronic intermittent restraint stress; restrained for 13 days for 3.5 h/day	6 days of daily exercise	What-When-Where task	Stress impaired neurogenesis and the "when" memory task, while exercise promoted neurogenesis and improved the "where" memory	The stressed exercising animals showed a larger increase in cell survival, maturation of new neurons in the dentate gyrus
Patki (2014) [62]	Animal	Sprague-Dawley rats	Experimental	Therapeutic	Social defeat model; seven encounters for 7 consecutive days	After stress exposure, engaged in treadmill exercise for 2 weeks (30 min/day)	Radial arm water maze	Stress impaired long-term memory (not short term), which was attenuated with exercise	Suppression of oxidative stress and inflammation. Modulation of deacetylation processes. Regulation of BDNF

Table 1 (continued)

Study	Animal/human	Subject characteristics	Study design	Preventive/therapeutic	Stress protocol	Exercise protocol	Memory assessment	Main findings	Speculated mechanisms
Patki (2014) [63]	Animal	Wistar rats	Experimental	Therapeutic	Single stress exposure (2 h restraint, 20 min forced swimming, 15 min rest, and 1–2 min diethyl ether exposure)	After stress exposure, exercised on treadmill for 2 weeks (30 min/day)	Radial arm water maze	Stress impaired memory, which was attenuated with exercise	Increase in BDNF and attenuation of HPA axis
Neves (2015) [64]	Animal	Wistar rats	Experimental	Preventive	Maternal deprivation, 3 h/day, 10 days	5 days/week of exercise, 50 min/day, for 8 weeks	Object recognition test, inhibitory avoidance test	Exercise prevented stress-induced memory impairment, for both short- and long-term memory	Exercise may attenuate stress-induced oxidative damage. The stress protocol increased lipid peroxidation, which was attenuated with exercise. Dopamine is metabolized by monoamine oxidase, producing hydrogen peroxide. Thus, increased dopamine turnover may induce oxidative stress, which may lead to cell death
Dief (2015) [65]	Animal	Wistar rats	Experimental	Preventive	Chronic immobilization stress for 10 days	6 weeks of swimming, 5 days/week	T-maze for spatial memory	Exercise attenuated stress-induced impairment in spatial memory	Stress protocol decreased BDNF levels; exercise increased BDNF levels, which may have prevented the stress-induced impairments. Exercise also increased Ach levels

Table 1 (continued)

Study	Animal/human	Subject characteristics	Study design	Preventive/therapeutic	Stress protocol	Exercise protocol	Memory assessment	Main findings	Speculated mechanisms
Kang (2015) [66]	Animal	C57BL/6 mice	Experimental	Preventive and therapeutic	6 h daily restraint for 3 weeks. Restraint occurred during weeks 5–8	Treadmill exercise (60 min/day, 5 days/week) occurred from week 1 to 8	Water maze task	Stress induced memory impairment, which was counter-regulated by exercise	Stress markedly reduced hippocampal CREB/BDNF signaling, which was reversed by 8 weeks of treadmill exercise
Ozbeyli (2015) [67]	Animal	Wistar rats	Experimental	Preventive	Exposure to cat odor	6 weeks of swimming, 5 days/week, 1 h/day	Object recognition task	Exercise had a protective effect against stress-induced memory decline	Decreasing oxidative damage parameters, such as lipid peroxidation, neutrophil infiltration and lucigenin activity
Radahmadi (2015) [68]	Animal	Wistar rats	Experimental	Preventive and therapeutic	21-day restraint stress, 6 h/day	Treadmill running 1 h/day for 21 days	Passive avoidance task	Exercise had both a preventive and therapeutic effect on stress-induced memory function, but a greater therapeutic effect was observed	Increased anti-oxidant enzymes, regulation of glucocorticoid receptors, increased neurotrophic factors, increased muscarinic receptor density, and increased acetylcholine release
Leem (2016) [69]	Animal	C57BL/6 mice	Experimental	Therapeutic	21-day restraint stress, 6 h/day	3 weeks of treadmill exercise, 1 h/day, 6 days/week	Y-maze and water maze task	Restraint stress produced learning and memory deficits, which were reversed with the 3-week exercise protocol	Exercise-induced expression of BDNF
Wearick-Silva (2016) [70]	Animal	Balb/c mice	Experimental	Therapeutic	Maternal separation during first 2 weeks of life	3-week running protocol, 60 min/day, 5 days/week	Object recognition task	Maternal separation impaired memory, which was reversed with exercise	Exercise-induced expression of BDNF

Table 1 (continued)

Study	Animal/human	Subject characteristics	Study design	Preventive/therapeutic	Stress protocol	Exercise protocol	Memory assessment	Main findings	Speculated mechanisms
Chen (2017) [71]	Animal	Thy1-H	Experimental	Therapeutic	Restraint stress; 1 h/day for 14 days	Treadmill exercise, 1 h/day, 14 days	Novel discrimination task	Stress protocol induced dendritic spine loss and memory impairment, which was rescued with exercise	Dendritic spine density and BDNF expression
dos Santos (2017) [72]	Animal	Wistar rats	Experimental	Preventive	Chronic variable stress; 24-h water deprivation, 1-3 h restraint, 24-h food deprivation, forced swimming, isolation, inclination of home cage, and damp bedding	20 min/day, 3 times/week, for 2 months	Inhibitory avoidance task	Stress protocol induced oxidative stress and impaired memory. Exercise prevented memory impairment	Exercise prevented stress-induced oxidative damage
Kochi (2017) [73]	Animal	Long-Evans rats	Experimental	Preventive	Social defeat paradigm	30 min of treadmill exercise for 14 days	Radial arm water maze	Exercise, prior to the trauma experience, mitigated memory impairment	Exercise prior to the stressor reduced anxiety levels from the stressor, which may have preserved memory function
Lapmanee (2017) [74]	Animal	Wistar rats	Experimental	Preventive	Restraint stress (varied, 1–8 weeks)	Voluntary wheel running for 4 weeks	Morris water maze and object recognition task	Exercise prevented impairments in memory	Exercise-induced BDNF expression
Leem (2017) [75]	Animal	C57BL/6 mice	Experimental	Concurrent; exercise and stress occurring together	Restraint stress; 6 h/day for 21 days	Treadmill running for 4 weeks	Morris water maze and object recognition task	Stress protocol impaired memory, which was attenuated with exercise	AMPA-receptor mediated mechanisms

Table 1 (continued)

Study	Animal/human	Subject characteristics	Study design	Preventive/therapeutic	Stress protocol	Exercise protocol	Memory assessment	Main findings	Speculated mechanisms
da Silva (2018) [76]	Animal	Wistar rats	Experimental	Preventive	Restraint stress with cylindrical acrylic tube	30 days of treadmill exercise, 30 min/day	Object recognition test	Exercise, coupled with virgin coconut oil, ameliorated the effects of stress on memory impairment	Preventive effects may occur from the antioxidant capabilities of exercise and coconut oil
Miller (2018) [77]	Animal	C57BL/6 mice	Experimental	Preventive and concurrent	5-min cold water swim on day 1, 30-min elevated platform stress on day 2, and 60-min restraint on day 3	4 weeks of voluntary wheel access	Radial arm maze	Stress alone impaired LTP and exercise alone increased LTP. Exercise with stress increased LTP more than stress only group. Exercise group made fewer errors in the memory task	Modulation of BDNF, TrkB, glucocorticoid, mineralocorticoid, and dopamine

immobilization/restraint, social defeat/competition and exposure to cat odor. All studies, except one (single session acute stress protocol), employed a chronic stress protocol (e.g., multiple repeated exposures over 1–2 weeks). All 23 studies employed a chronic exercise protocol (e.g., daily exercise from 2 to 8 weeks; either forced treadmill exercise or voluntary wheel access). Among the 23 studies, the commonly assessed memory tasks included the Morris water maze, object recognition test, or inhibitory avoidance task.

Eight studies evaluated a preventive model (i.e., exercise occurring prior to stress-induction), three employed a concurrent model (exercise bout occurred during or around the same time as the stress protocol), ten studies employed a therapeutic model (i.e., exercise occurring after stress-induction), and two studies evaluated both a preventive and therapeutic model within the same study.

Among the eight studies employing a preventive model, all eight demonstrated that the stress regimen impaired memory function. In all eight of these studies, when exercise occurred prior to the stressor, exercise attenuated the stress-induced memory impairment effect.

Among the ten studies employing a therapeutic model, one study showed that the stress protocol enhanced memory function, one showed that the stress protocol did not influence memory, and eight demonstrated that the stress regimen impaired memory function. Among the eight studies showing that the stress protocol impaired memory function, all eight studies demonstrated that exercise, after the stressor, attenuated stress-induced memory impairment.

Among the three concurrent models, and the two studies that evaluated both preventive and therapeutic effects, all showed that the stress protocol impaired memory function. Among the three concurrent models, two demonstrated a beneficial effect of exercise in mitigating stress-induced memory impairment. Among the two studies employing both a preventive and therapeutic model, both demonstrated attenuation effects of exercise on stress-induced memory impairment.

Discussion

The objective of this systematic review was to evaluate the potential preventive and therapeutic effects of exercise in attenuating stress-induced memory impairment. There was consistent evidence that chronic exercise had both a preventive and therapeutic effect in mitigating chronic stress-induced memory impairment. The narrative that follows will discuss these mechanistic pathways, as displayed in Fig. 1. For additional discussion on these mechanisms, the reader is referred elsewhere [16, 27, 28].

Acute stress and memory

Acute moderate levels of stress may enhance memory, particularly emotional-based information (vs neutral stimuli). Specifically, enhanced encoding and consolidation of stimuli is more likely to occur for information perceived as "high priority" [29–33]. The stressor, occurring prior to the memory task, may help to augment attentional resources (via, for example, the prefrontal and parietal structures) to the memory stimuli and, in turn, enhance encoding of the information [34, 35]. In addition to psychological stress, emerging work also suggests that exercise-induced physiological arousal may help to subserve stress-related memory function (emotional memory) [36]. Additional work is needed to determine whether there is an additive effect of exercise and acute stress on memory function.

Additionally, the stressor (including exercise) [36], occurring before, or shortly after, the memory task can help to facilitate the consolidation of the memory trace. For example, cortisol crosses the blood–brain barrier and binds to mineralocorticoid or glucocorticoid receptors. After which, PKA activation may help to facilitate exocytosis of AMPA receptors (and activation of NMDA receptors) [37], subserving hippocampal LTP [38]. Acute stress may also induce levels of epinephrine, activating the vagus nerve and, in turn, facilitating LTP via neurotransmitter (e.g., norepinephrine, dopamine, serotonin, and acetylcholine) production to the hippocampus [39–42]. To illustrate, the vagus nerve may stimulate the production of norepinephrine from the locus coeruleus, which then binds to adrenergic receptors, ultimately facilitating a cascade of intracellular signaling to induce synaptic plasticity [43]. Moreover, cortisol may augment endocannabinoid levels, binding to CB1 receptors in GABA interneurons and, ultimately, inhibiting GABA neurotransmitter levels [44]. This, in turn, may help to preserve memory, as GABA inhibition may help facilitate LTP [45] and GABA receptor activation may impair memory [46].

Although acute stress, occurring before encoding or during the early stages of consolidation, can facilitate encoding and consolidation of the prioritized stimuli, it can have the opposite effect on non-prioritized stimuli. The encoding of the stressful event may compete with the encoding of non-relevant or non-prioritized stimuli. Further, if the stressor occurs around the period of retrieving a memory, this memory retrieval process can be impaired, as attentional resources are shifted away from retrieval processes to encoding the stressful event. Additionally, inactive synapses, representing previously encoded stimuli, may become de-potentiated when LTP increases in other synapses [28]. Moreover, during the stressor, reduced neuronal firing may occur in the prefrontal cortex, which may impair memory retrieval since the prefrontal cortex plays an important role in such retrieval processes [47]. It would be worthwhile to investigate whether acute exercise can attenuate these effects by, for example, attenuating the stress response and facilitating emotional regulation [5].

Taken together, acute moderate levels of stress may help to facilitate encoding and consolidation of prioritized stimuli (particularly emotional stimuli), whereas extreme acute stressors may detrimentally influence retrieval of memories when the stressor occurs around the time of retrieving an unrelated memory. Notably, and as discussed next, chronic elevations in cortisol, lasting more than a few hours, can impair memory function (inducing LTD) [38].

Chronic stress and memory

Chronic stress may detrimentally influence stress through various mechanisms, including enhanced HPA axis activity. Over time, this may impair cell survival and neuronal morphology (e.g., loss of spines, shrinkage of dendrites) [4]. Regarding cell survival, astrocytes, which support the survival of neurons, possess glucocorticoid receptors and are significantly affected by chronic psychosocial stress [48]. Considering neuronal morphology, reduced synaptic firing, via LTD for example, causes actin loss and dendritic spine shrinkage [49]. Further, chronic stress may reduce BDNF levels [50], which play an important role in facilitating signaling pathways (e.g., RAC1) that stabilize dendritic spines [51]. Additionally, chronic stress may reduce neurotransmitter levels (e.g., dopamine) [52], decrease AMPA receptor expression [53], and downregulate mineralocorticoid and glucocorticoid receptor expression [54]. This downregulation and desensitization of these receptors may prevent activation of some of the above-mentioned cellular pathways (e.g., PKA) that may facilitate LTP. Further, chronic stress may inhibit neurogenesis, and ultimately, hippocampal volume loss, via, for example, apoptosis of progenitor cells to cell cycle arrest [49].

Exercise mitigates negative effects of chronic stress

Exercise may attenuate the memory-related consequences of chronic stress via various pathways. Ultimately, exercise may help to facilitate LTP through induced neuronal excitability, via stimulation of the vagus nerve as well as muscle afferent nerve fibers [55], which have direct projections to the brainstem and, ultimately, the hippocampus. Further, exercise-induced alterations in hormones (e.g., epinephrine and cortisol) can also influence neuronal excitability. Facilitating these effects, exercise has been shown to enhance neurotrophic factors (e.g., BDNF), induce transcription factors (e.g., CREB) expression, and increase AMPA trafficking [55]. Exercise may also help attenuate chronic stress-induced memory impairment via attenuation of HPA axis activity, suppress oxidative stress, facilitate neurogenesis,

and regulate mineralocorticoid and glucocorticoid receptor expression [27].

Conclusion

This review demonstrates that, within animal models, chronic stress is associated with memory impairment and chronic exercise has both a preventive and therapeutic effect in attenuating stress-induced memory impairment. Given the paucity of work among human studies, future work on this topic among humans should investigate, specifically, whether exercise has a preventive and therapeutic effect in mitigating memory impairment caused from psychophysiological stress. Such work should also consider models that evaluate acute exercise and acute stress protocols. Further, work should also evaluate varying parameters of exercise, such as the intensity, duration, and type of exercise, as variations of these dimensions may have a unique influence on potentially attenuating stress-induced memory impairment.

Compliance with ethical standards

Conflict of interest Author PL declares no conflict of interest. Author EF declares no conflict of interest.

Research involving human participants All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent No consent was needed as this is a review paper.

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